

CLAIMS

1. A method for determining an inflammatory disease, which comprises detecting at least one gene polymorphism existing in at least one gene selected from the group consisting of a lymphotoxin- α (LT- α) gene, an I Kappa B-like (IKBL) gene, and a BAT1 gene.

2. A method for determining an inflammatory disease, which comprises detecting at least one single nucleotide polymorphism existing in at least one gene selected from the group consisting of the lymphotoxin- α (LT- α) gene, the I Kappa B-like (IKBL) gene, and the BAT1 gene.

3. A method for determining an inflammatory disease, which comprises detecting at least one single nucleotide polymorphism selected from the group consisting of the following (1) to (5):

(1) a G/A polymorphism at nucleotide 10 in the nucleotide sequence of exon 1 of the LT- α gene shown in SEQ ID NO: 1;

(2) an A/G polymorphism at nucleotide 90 in the nucleotide sequence of intron 1 of the LT- α gene shown in SEQ ID NO: 2;

(3) a C/A polymorphism at nucleotide 81 in the nucleotide sequence of exon 3 of the LT- α gene shown in SEQ ID NO: 3;

(4) a T/A polymorphism at nucleotide 572 in the nucleotide sequence of a promoter of the IKBL gene shown in SEQ ID NO: 4; and

(5) a G/C polymorphism at nucleotide 1228 in the nucleotide sequence of a promoter of the BAT1 gene shown in SEQ ID NO: 5.

4. A method for determining an inflammatory disease, which comprises detecting whether or not the combination of the nucleotide 10 in the nucleotide sequence of exon 1 of the LT- α gene shown in SEQ ID NO: 1 and the nucleotide 90 in the nucleotide sequence of intron 1 of the LT- α gene shown in SEQ ID NO: 2 is G-A heterozygote, A-G heterozygote or A-A homozygote.

5. A method for determining an inflammatory disease, which comprises

detecting a gene polymorphism whereby an amino acid to be encoded is mutated from threonine to asparagine by substitution of at least one of the nucleotides 80 to 82 in the nucleotide sequence of exon 3 of the LT- α gene shown in SEQ ID NO: 3 with another nucleotide.

6. The method according to any of claims 1 to 5 wherein the inflammatory disease is myocardial infarction.

7. An oligonucleotide that can hybridize to a sequence of at least 10 continuous nucleotides containing at least one position selected from the group consisting of the following (1) to (5), the position being contained in the sequences shown in SEQ ID NOS: 1 to 5, or to a complementary sequence thereof, and is used as a probe in the method of any of claims 1 to 6:

(1) position 10 of the nucleotide sequence of exon 1 of the LT- α gene shown in SEQ ID NO: 1;

(2) position 90 of the nucleotide sequence of intron 1 of the LT- α gene shown in SEQ ID NO: 2;

(3) position 81 of the nucleotide sequence of exon 3 of the LT- α gene shown in SEQ ID NO: 3;

(4) position 572 of the nucleotide sequence of the promoter of the IKBL gene shown in SEQ ID NO: 4; and

(5) position 1228 of the nucleotide sequence of the promoter of the BAT1 gene shown in SEQ ID NO: 5.

8. An oligonucleotide that can amplify a sequence of at least 10 continuous nucleotides containing at least one position selected from the group consisting of the following (1) to (5), the position being contained in the sequences shown in SEQ ID NOS: 1 to 5, and/or to a complementary sequence thereof, and is used as a primer in the method of any of claims 1 to 6:

(1) position 10 of the nucleotide sequence of exon 1 of the LT- α gene shown in SEQ ID NO: 1;

(2) position 90 of the nucleotide sequence of intron 1 of the LT- α gene shown in

SEQ ID NO: 2;

(3) position 81 of the nucleotide sequence of exon 3 of the LT- α gene shown in SEQ ID NO: 3;

(4) position 572 of the nucleotide sequence of the promoter of the IKBL gene shown in SEQ ID NO: 4; and

(5) position 1228 of the nucleotide sequence of the promoter of the BAT1 gene shown in SEQ ID NO: 5.

9. The oligonucleotide according to claim 8 wherein the primer is forward primer and/or reverse primer.

10. A kit for diagnosing an inflammatory disease, which comprises 1 or more types of the oligonucleotide of any of claims 7 to 9.

11. The kit according to claim 10 wherein the inflammatory disease is myocardial infarction.

12. A method for analyzing the expression state of LT- α , IKBL, or BAT1, which comprises detecting at least one single nucleotide polymorphism selected from the group consisting of the following (1) to (5).

(1) a G/A polymorphism at nucleotide 10 in the nucleotide sequence of exon 1 of the LT- α gene shown in SEQ ID NO: 1;

(2) an A/G polymorphism at nucleotide 90 in the nucleotide sequence of intron 1 of the LT- α gene shown in SEQ ID NO: 2;

(3) a C/A polymorphism at nucleotide 81 in the nucleotide sequence of exon 3 of the LT- α gene shown in SEQ ID NO: 3;

(4) a T/A polymorphism at nucleotide 572 in the nucleotide sequence of a promoter of the IKBL gene shown in SEQ ID NO: 4; and

(5) a G/C polymorphism at nucleotide 1228 in the nucleotide sequence of a promoter of the BAT1 gene shown in SEQ ID NO: 5.

13. A method for measuring the transcriptional activity of LT- α , IKBL, or BAT1, which comprises introducing an LT- α , IKBL, or BAT1 gene fragment containing at least one single nucleotide polymorphism selected from the group

consisting of the following (1) to (5) into a cell, culturing the cell, and analyzing the expression of the gene.

- (1) a G/A polymorphism at nucleotide 10 in the nucleotide sequence of exon 1 of the LT- α gene shown in SEQ ID NO: 1;
- (2) an A/G polymorphism at nucleotide 90 in the nucleotide sequence of intron 1 of the LT- α gene shown in SEQ ID NO: 2;
- (3) a C/A polymorphism at nucleotide 81 in the nucleotide sequence of exon 3 of the LT- α gene shown in SEQ ID NO: 3;
- (4) a T/A polymorphism at nucleotide 572 in the nucleotide sequence of a promoter of the IKBL gene shown in SEQ ID NO: 4; and
- (5) a G/C polymorphism at nucleotide 1228 in the nucleotide sequence of a promoter of the BAT1 gene shown in SEQ ID NO: 5.

14. A method for screening for a substance inhibiting the transcriptional activity of LT- α , IKBL, or BAT1, which comprises introducing an LT- α , IKBL, or BAT1 gene fragment containing at least one single nucleotide polymorphism selected from the group consisting of the following (1) to (5) into a cell, culturing the cell in the presence of a candidate substance inhibiting the transcriptional activity of LT- α , IKBL, or BAT1, and analyzing the expression of the gene.

- (1) a G/A polymorphism at nucleotide 10 in the nucleotide sequence of exon 1 of the LT- α gene shown in SEQ ID NO: 1;
- (2) an A/G polymorphism at nucleotide 90 in the nucleotide sequence of intron 1 of the LT- α gene shown in SEQ ID NO: 2;
- (3) a C/A polymorphism at nucleotide 81 in the nucleotide sequence of exon 3 of the LT- α gene shown in SEQ ID NO: 3;
- (4) a T/A polymorphism at nucleotide 572 in the nucleotide sequence of a promoter of the IKBL gene shown in SEQ ID NO: 4; and
- (5) a G/C polymorphism at nucleotide 1228 in the nucleotide sequence of a promoter of the BAT1 gene shown in SEQ ID NO: 5.

15. A substance inhibiting the transcriptional activity of LT- α , IKBL, or

BAT1, which is obtained by the screening method of claim 14.

16. The method according to claim 13 or 14, which comprises introducing a transcriptional unit wherein a reporter gene is ligated downstream of said LT- α , IKBL, or BAT1 gene fragment into a cell, culturing the cell, and analyzing the expression of the gene by measuring the reporter activity.

17. The method according to claim 16, wherein said reporter gene is luciferase gene.

18. A method for screening for a transcriptional regulatory factor of LT- α , IKBL, or BAT1, which comprises bringing a gene fragment containing at least one single nucleotide polymorphism selected from the group consisting of the following (1) to (5) into contact with a sample wherein a transcriptional regulatory factor of LT- α , IKBL, or BAT1 is presumed to be present, and detecting binding of the above fragment with the transcriptional regulatory factor.

(1) a G/A polymorphism at nucleotide 10 in the nucleotide sequence of exon 1 of the LT- α gene shown in SEQ ID NO: 1;

(2) an A/G polymorphism at nucleotide 90 in the nucleotide sequence of intron 1 of the LT- α gene shown in SEQ ID NO: 2;

(3) a C/A polymorphism at nucleotide 81 in the nucleotide sequence of exon 3 of the LT- α gene shown in SEQ ID NO: 3;

(4) a T/A polymorphism at nucleotide 572 in the nucleotide sequence of a promoter of the IKBL gene shown in SEQ ID NO: 4; and

(5) a G/C polymorphism at nucleotide 1228 in the nucleotide sequence of a promoter of the BAT1 gene shown in SEQ ID NO: 5.

19. The method according to claim 18 wherein the detection is carried out by gel shift assay.

20. A method for evaluating ability to induce an adhesion molecule in a cell, which comprises introducing a gene fragment containing a C/A polymorphism at nucleotide 90 in a nucleotide sequence of intron 1 of an LT- α gene shown in SEQ ID NO: 2 into a cell in which an adhesion molecule can be induced, and

evaluating the ability to induce an adhesion molecule in the cell.

21. The method according to claim 20 wherein said cell is human coronary-artery smooth-muscle cell (HCASMC).

22. The method according to claim 20 wherein said adhesion molecule is vascular cell-adhesion molecule-1 (VCAM-1) or E-selectin.

23. A method for treating an inflammatory disease, which comprises suppressing the expression or activity of lymphotoxin- α (LT- α).

24. The method according to claim 23 wherein the inflammatory disease is myocardial infarction.

25. The method according to claim 23 or 24 wherein an antibody against lymphotoxin- α (LT- α) is used.

26. A therapeutic agent for an inflammatory disease, which comprises as an active ingredient a substance suppressing the expression or activity of lymphotoxin- α (LT- α).

27. The therapeutic agent according to claim 26 wherein the substance suppressing the expression or activity of lymphotoxin- α (LT- α) is an antibody against lymphotoxin- α .

28. A method for screening for a therapeutic agent for an inflammatory disease, which comprises the steps of bringing a cell into contact with a candidate substance, analyzing the expression level of a gene encoding lymphotoxin- α (LT- α) within the cell, and selecting as a therapeutic agent for an inflammatory disease a candidate substance that lowers the expression level of the gene by comparison with a condition where the candidate substance is absent.

29. A method for screening for a therapeutic agent for an inflammatory disease, which comprises the steps of bringing lymphotoxin- α (LT- α) into contact with a candidate substance, measuring the activity of lymphotoxin- α , and selecting as a therapeutic agent for an inflammatory disease a candidate substance that lowers the activity of lymphotoxin- α by comparison with a condition where the candidate substance is absent.

30. The method according to claim 29 wherein the activity of lymphotoxin- α is an activity to induce an adhesion molecule and/or a cytokine.

31. The method according to claim 30 wherein the adhesion molecule is VCAM-1, ICAM-1, or E-selectin, and the cytokine is TNF.

32. The method according to claim 28 or 29 wherein the expression level or activity of lymphotoxin- α (LT- α) is lowered through an increase in the expression level or activity of the IKBL gene.